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Comparison of Pleuropneumonectomy and Limited Surgery for Lung Cancer With Pleural Dissemination

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The role of surgery in the management of lung cancer with pleural dissemination is controversial. We performed a retrospective analysis of our patients with lung cancer and pleural dissemination who were treated surgically. Between 1973 and 1993, 1,206 patients with lung cancer underwent pulmonary resection at Kanazawa University Hospital. Among them, 40 (3.3%) had pleural dissemination without pleural effusion. The 1-, 3-, and 5-year survival rates for 38 patients (except 2 patients undergoing exploratory thoracotomy alone) were 51.5%, 19.4%, and 19.4%, respectively. The 1-year survival rate in the 10 patients who underwent pleuropneumonectomy was only 20%, and 9 of these patients died within 18 months postoperatively (1 patient has survived for 25 months). In contrast, the 1-, 3-, and 5-year survival rates for the 14 patients who underwent resection of the primary tumor plus parietal pleurectomy were 85.1%, 35.5%, and 35.5%, respectively, a significantly better outcome ($P < 0.01$). Seven patients are still alive (the longest survival time is 65 months with the disease). The average survival time in the seven fatal cases was 18 months. In patients with lung cancer accompanied by pleural dissemination, it is quite possible that local excision plus pleurectomy will be justified.

KEY WORDS: **lung cancer, pleural dissemination, pleuropneumonectomy, limited operation, pleurectomy**

INTRODUCTION

Lung cancer associated with carcinomatous pleurisy is generally already near the terminal stage. There are usually no indications for surgery, so conservative treatment is provided, chiefly to control the patient's pleural effusion [1–3]. In some cases, however, carcinomatous pleurisy is found at the stage of pleural dissemination alone without pleural effusion. Unfortunately, it is difficult to achieve the complete resection of lung cancer accompanied by pleural dissemination, so the prognosis is usually poor even when patients are treated surgically. In addition, there is still controversy regarding the optimal operative procedure for lung cancer with pleural dissemination. Accordingly, we evaluated the effect of extending the operative procedure by comparing the results of extended and limited surgery.

PATIENTS AND METHODS

Among the 1,206 patients with lung cancer who underwent surgery at Kanazawa University Hospital during the 21-year period from 1973 to 1993, 40 patients (3.3%)

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were diagnosed pathologically as having lung cancer with pleural dissemination and were included in this study. Patients with carcinomatous pleurisy who had a positive result on cytological examination of their pleural effusion were excluded, since they were all treated by tube drainage plus intrathoracic instillation of anticancer agents and OK-432 (Picibanil; Chugai Co., Tokyo), an immunostimulator. There were 19 men and 21 women aged from 32 to 81 years, with an average age of 61 years. Adenocarcinoma was the most prevalent histological type, and was found in 33 patients (82.5%). The other histological types included squamous cell carcinoma in five patients, large cell carcinoma in one patient, and adenosquamous carcinoma in one patient.

Assignment to the T and N categories was made according to the Union Internationale Contre le Cancer (UICC) TNM staging system [4]. Namely, tumor foci in the ipsilateral parietal and visceral pleura that were discontinuous from direct pleural invasion by the primary tumor were classified T4. Direct extension to parietal pleura was classified T3. However, intrapulmonary metastasis was designated as M positive according to the TNM staging system of the Japan Lung Cancer Society [5], which is fairly different from the American Joint Committee on Cancer (AJCC) stage criteria for intrapulmonary metastasis [6]. Accordingly, we defined intrapulmonary metastasis as a tumor lesion that was completely isolated (grossly or microscopically) from the main lesion and was histologically identical to it. The postoperative stage was stage IIIB or stage IV, since all patients with pleural dissemination were classified as T4. Thirty-one patients (77.5%) were classified as stage IIIB, with 11 being diagnosed as N0, 3 as N1, 13 as N2, and 4 as N3 (all of them had the contralateral mediastinal nodal metastasis). Most of the operations for N3 disease were done via a median sternotomy. There were nine patients (22.5%) with stage IV disease and all of them had intrapulmonary metastasis. One patient was classified as N0, two as N1, five as N2, and one as N3 (contralateral mediastinal nodal metastasis).

As a rule, the operative method was determined by the size of the primary tumor. Resection of the primary tumor with parietal pleurectomy was employed as a limited operation for patients in whom resection of the primary could be achieved with partial resection of the lung. Lobectomy with parietal pleurectomy was employed for patients in whom it was judged to be necessary for resection of the primary tumor, and pleuropneumonectomy as an extended operation was performed when pneumonectomy was deemed necessary for resection of the primary. Ten patients underwent an extended operation, 14 underwent lobectomy with parietal pleurectomy, and 14 underwent limited surgery. In addition, exploratory thoracotomy alone was performed in two patients. Generally speaking, most patients in the pleuropneumonectomy group had large tumors and nodal metastases, while most patients in the limited surgery group had small tumors and no nodal metastases (Table I). In other words, there were differences in patient background factors between the various groups. Postoperatively, adriamycin (ADM) and a streptococcal preparation (OK-432) were instilled into the pleural cavity through a thoracic tube in all patients. A combination of cisplatin (CDDP) and vindesine (VDS) was used as systemic chemotherapy since 1986, whereas before that multidrug combination therapy using ADM as the main agent was employed. All of the patients in the limited operation group were treated using the CDDP plus VDS protocol, while half of those in the extended operation group underwent treatment with the earlier protocol.

The survival rate was calculated by the Kaplan-Meier method [7]. Statistical significance was evaluated by the generalized Wilcoxon test [8] for survival rates and by analysis of variance (ANOVA) for the other data. A probability value of less than 0.05 was regarded as statistically significant.

RESULTS

The duration of surgery was 228 ± 58 minutes in the pleuropneumonectomy group, 170 ± 47 minutes in the lobectomy group, and 144 ± 35 minutes in the limited operation group. The pleuropneumonectomy group required the longest operation time and the difference was significant. The intraoperative blood loss was 1,943 ± 1,069 ml in the pleuropneumonectomy group, 567 ± 352 ml in the lobectomy group, and 428 ± 366 ml in the limited operation group, and was significantly greater in the pleuropneumonectomy group than in the other groups (Fig. 1).

The overall 1-, 3-, and 5-year survival rates for 38 patients in this series (except 2 patients undergoing exploratory thoracotomy alone) were 51.5%, 19.4%, and 19.4%, respectively, with a median survival time of 17 months. Reviewing survival in relation to the operative procedure employed, the 1-year survival rate in the 10 patients who underwent pleuropneumonectomy was only 20%, a poor outcome. Nine of these patients died within 18 months after surgery, while one patient has survived for 25 months. On the other hand, among the 14 patients who underwent limited surgery, the 1-, 3-, and 5-year survival rates were 85.1%, 35.5%, and 35.5% respectively. Seven of these patients are still alive (the longest survivor has lived for 65 months despite local and distant recurrence). The average survival time in the seven fatal cases was 18 months. When the survival rates of the pleuropneumonectomy and limited operation groups were compared, the rate was found to be significantly better in the limited operation group. For the 14 patients in the lobectomy group, the 1- and 2-year survival rates were 42.9% and 35.7%, i.e., higher than in the pleuropneumo-

TABLE I. Clinical Profile of Patients With Lung Cancer Accompanied by Pleural Dissemination*

	I. Pleuropneumonectomy (N = 10)	II. Lobectomy (N = 14)	III. Limited surgery (N = 14)	I vs. III *P* values
Age (years) (range)	52 ± 13.1 (32–70)	66 ± 8.9 (45–79)	62 ± 8.9 (48–77)	$P < 0.05$
Sex				
Male	8	6	3	$P < 0.05$
Female	2	8	11	
Stage				
IIIB	9	11	10	NS
IV	1	3	4	
Tumor size (mm) (range)	50.3 ± 25.4 (20–90)	47.1 ± 16.1 (25–85)	30.1 ± 9.4 (18–50)	$P < 0.05$
Nodal metastasis				
N0	2	3	7	$P = 0.063$
N1	1	2	1	
N2	3	8	6	
N3	4	1	0	
Histological type				
Adenocarcinoma	8	12	11	NS
Squamous cell carcinoma	1	2	2	
Adenosquamous carcinoma	0	0	1	
Large cell carcinoma	1	0	0	

* Limited surgery = resection of the primary tumor with parietal pleurectomy. NS, not statistical.

nectomy group but lower than in the limited operation group (Fig. 2).

The T4N0M0 patients and the T4N1-3M0/ T4M1 patients had 1-, 3-, and 5-year survival rates of 90.9%, 57.7%, and 57.7% vs. 34.9%, 7.8%, and nil, respectively, with significantly better results in the former group (Fig. 3).

There were three patients who survived for 3 years or more and the longest survival time was 65 months. All of these patients underwent limited surgery. Histological examination revealed adenocarcinoma in all. Two of these patients were classified as N0 and one was classified as N2, while all three were classified as M0 (Table II).

DISCUSSION

Pleural dissemination as a form of extrapulmonary spread of lung cancer has been difficult to diagnose preoperatively, since it is not easy to visualize the parietal or visceral pleura by ordinary imaging methods. Dissemination is thus often detected intraoperatively or after pleural effusion develops with the progression of pleural involvement. However, some recent papers have described the diagnosis of pleural dissemination by thin-slice computed tomography (CT) [9,10] and it appears possible to detect pleural dissemination before effusion develops.

In most patients with malignant pleural effusion, i.e., carcinomatous pleurisy, not only the tumor itself but also lymphatic metastases show considerable progression. Treatment emphasizes control of the pleural effusion, but the therapeutic results are generally poor. Few patients survive 2 years or more, and many of them die within 1 year after the start of treatment. In contrast, pleural dissemination unassociated with a pleural effusion is not thought to be a hopeless condition, so the detection of lesions at the stage of pleural dissemination without effusion is expected to contribute to a better outcome.

Pleuropneumonectomy was first described by Harris et al.[11] as a method of curative resection for pleural malignant mesothelioma, and it was evaluated again by Butchart et al.[12] for the curative resection of diffuse pleural malignant mesothelioma. Using this procedure, the primary lesion in the lung is resected en bloc with the disseminated pleural lesions. Although this procedure was hoped to achieve curative resection, most patients died of distant metastasis, contrary to our expectation. In fact, none of our patients undergoing pleuropneumonectomy, which is associated with major surgical invasion, achieved 3-year survival. As the reasons for this poor outcome, we can point out that there were many male patients, many young patients, many with large tumors, and many with progressive lymph node metastasis in the pleuropneumonectomy group.

Since extended surgery thus cannot be expected to provide curative resection in patients with lung cancer accompanied by pleural dissemination, it is necessary to determine whether the survival rate can be improved by limited surgery, which is considered to be less than curative. Pleurectomy involves extended resection of the parietal pleura (excluding the diaphragmatic area) to prevent pleural effusion and produce adhesions between the visceral pleura and the chest wall or mediastinum. This procedure was first advocated by Beattie [13] and Jensik et al.[14]. Although it was found to be effective in the treatment of carcinomatous pleurisy due to metastatic breast cancer, they reported that its efficacy for carcinomatous pleurisy secondary to lung cancer was doubtful.

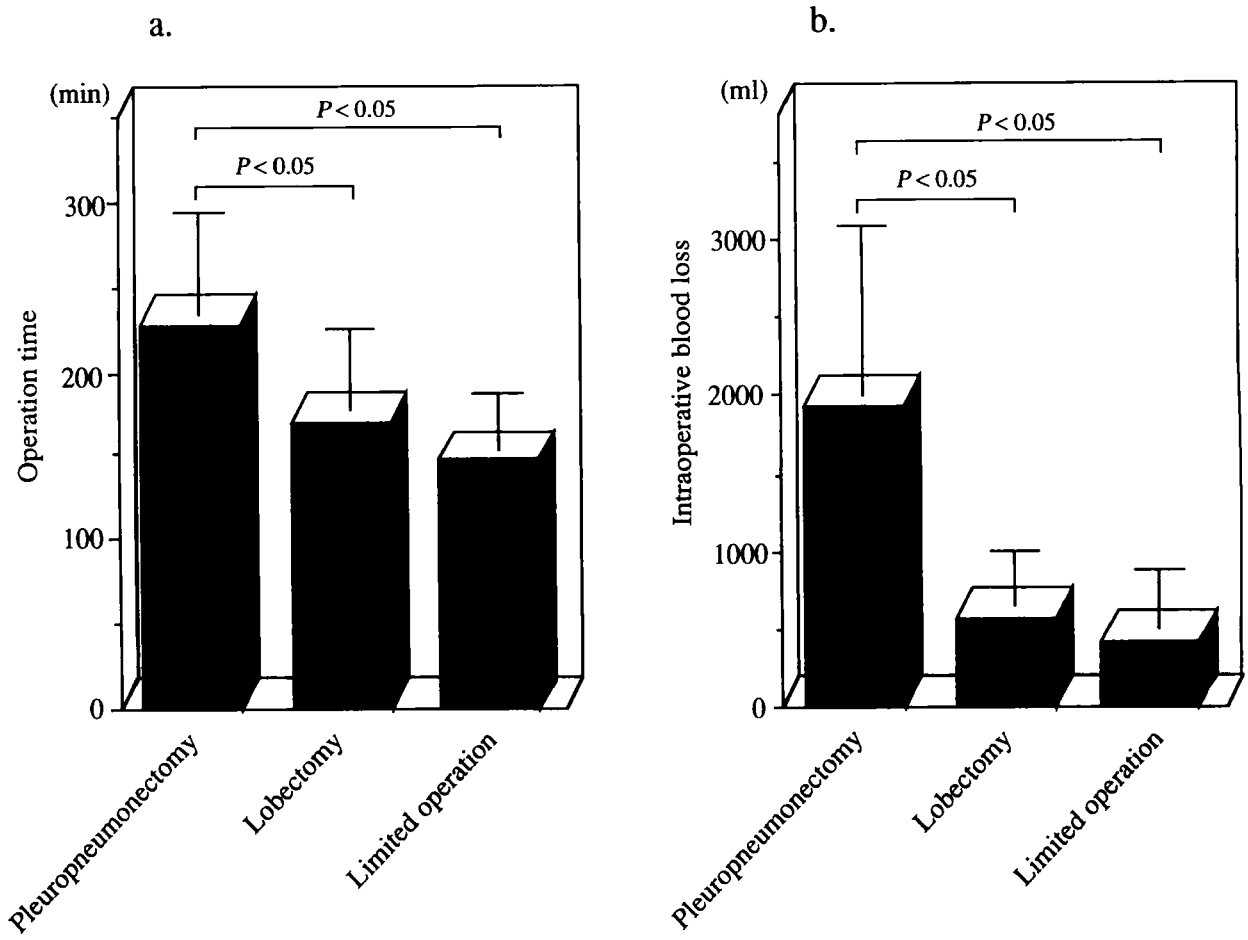

Fig. 1. Comparison of operation time (**a**) and intraoperative blood loss. (**b**). There was a significant difference ($P < 0.05$) between the pleuropneumonectomy group and the other groups.

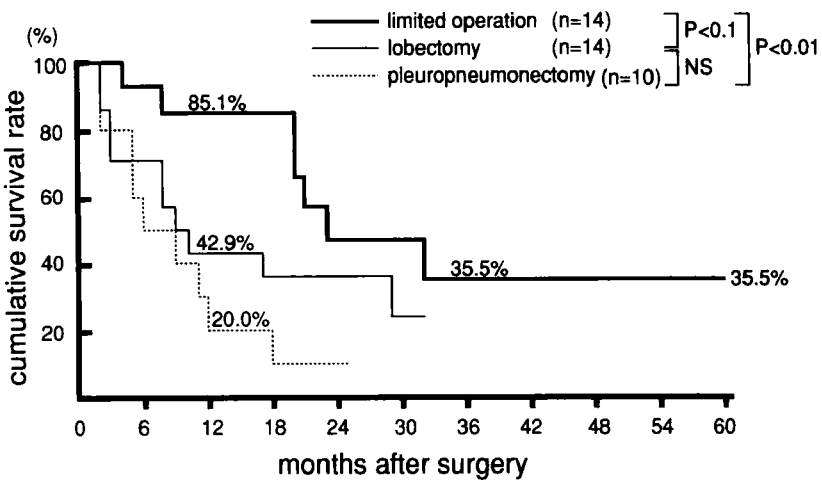

Fig. 2. Postoperative survival of patients with lung cancer accompanied by pleural dissemination according to surgical procedure. There was a significant difference ($P < 0.01$) between the limited operation group (n = 14, heavy line) and the pleuropneumonectomy group (n = 10, dotted line).

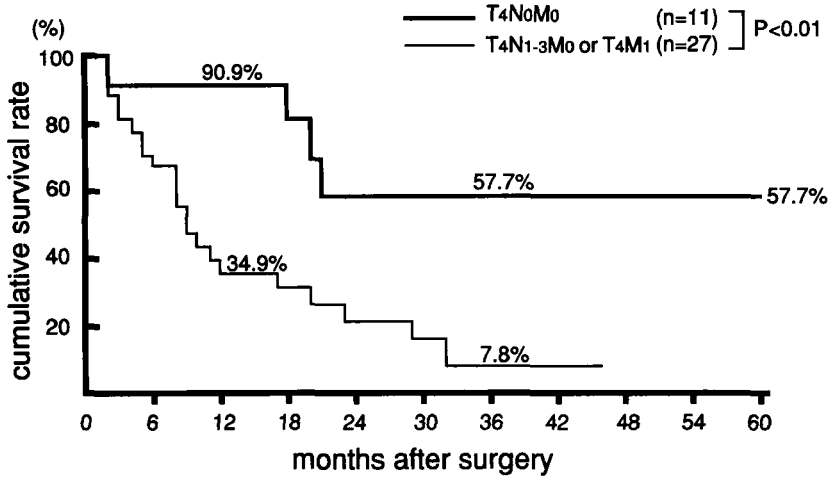

Fig. 3. Effect of TNM status on survival rates in patients with lung cancer accompanied by pleural dissemination. When T4N0M0 tumors (n = 11, heavy line) were compared with T4N1-3 or T4M1 (n = 27, thin line), there was a significant difference ($P < 0.01$) between the patients with T4N0M0 disease and T4N1-3 or T4M1 disease.

TABLE II. Patients Surviving More Than 3 Years After Surgery for Lung Cancer With Pleural Dissemination

Patient no.	Age (years)	Sex	Histological type	TNM	Operation	Survival (months)	Outcome
1	64	F	Adenocarcinoma	T4N0M0	Limited	65	Alive
2	49	M	Adenocarcinoma	T4N2M0	Limited	46	Alive
3	63	F	Adenocarcinoma	T4N0M0	Limited	42	Alive

Martini et al. [15] performed pleurectomy in 41 patients with carcinomatous pleurisy due to lung cancer, and the 1-, 2-, and 3-year survival rate was 23%, 12%, and 3%, respectively, with a median survival time of 6 months. Although the long-term prognosis was poor, they found that pleural fluid did not accumulate again and that the procedure was effective in controlling malignant pleural effusion. Failure of pleurectomy to achieve long-term survival might be explained by the fact that all these patients had carcinomatous pleurisy accompanied by malignant pleural effusion, and that the primary tumor was left in situ after pleurectomy alone. Whether prolonged survival is achieved or not by patients without pleural effusion thus depends on how well progression of the primary lesion is controlled.

We have recently employed resection of the primary tumor with parietal pleurectomy as the standard operative procedure. The present study showed that the survival rate was significantly better in the limited operation group compared to the pleuropneumonectomy group. In addition, the operating time was significantly shorter and the intraoperative blood loss was significantly less in the limited operation group. In these respects, it appears that this limited procedure can be recommended for lung cancer with pleural dissemination. We believe that the primary lesion should only be resected when it is located near the periphery of the lung and can be removed by wedge resection. This is because resections that are more extensive than lobectomy prevent the development of adhesions to the chest wall due to expansion of the lung, making the future control of pleural effusion impossible. In our limited operation group, no postoperative pleural effusions were detected in any of the patients. For the improvement of limited surgery in the future, it is necessary to control residual disseminated lesions remaining in the visceral pleura. If some effective therapeutic method is established for the visceral pleura, the number of patients indicated for limited surgery will increase further. In this regard, we have employed intrapleural instillation of sclerosing agents such as ADM and OK-432 through a thoracic tube, because ADM is known to be one of the most effective drugs against lung cancer and OK-432 is known to promote pleural adhesion by the development of fibrin clots. In addition, intraoperative intrapleural hypotonic treatment with CDDP [16] appears to be promising and worthy of further study.

CONCLUSIONS

Although the difference in outcome was not entirely attributable to differences in the operative procedure, the

employment of extended surgery cannot be justified in patients with lung cancer accompanied by pleural dissemination. In contrast, the limited operation that we currently use achieves a relatively good outcome. However, this might be because patients with slowly growing tumors or those responding to chemotherapy were eventually selected as the limited operation group. In conclusion, surgery for lung cancer accompanied by pleural dissemination should be restricted to patients in whom it is possible to perform a limited operation. We hope to conduct further studies in a larger series of patients. In particular, we believe that T4N0M0 patients may benefit from this operative procedure.

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